Islet Cell Transplantation

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An estimated 177 million people worldwide suffer from diabetes. Insulin administration controls the day-to-day problems of this disease but glucose homeostasis is not fully normalized with insulin replacement and the long-term complications caused by suboptimal homeostasis are significant. In terms of transplantation, two options exist: whole organ pancreas transplant and isolated islet cell transplant. Whole organ transplantation is favored in patients who also need kidney transplantation or have exocrine deficiency. Islet cell transplantation is usually reserved for patients with brittle diabetes and hypoglycemic unawareness. In this latter group of patients, this procedure can be lifesaving. Additionally, it has a profound beneficial effect on quality of life and secondary complications of diabetes such as neuropathy and nephropathy.

ISLET CELL TRANSPLANT

Preprocedure

Prior to the procedure, Doppler evaluation of the liver is performed to confirm patency of the hepatic artery, portal vein, and hepatic veins. Antibacterial, antifungal, and antiviral prophylaxis is administered. Islet cells are harvested by the transplant team and checked for purity.

Procedure

The patient's blood pressure, heart rate and rhythm, and oxygen saturation are monitored noninvasively. Conscious sedation is provided using fentanyl and midazolam. The anterior and right lateral abdomen is prepared using chlorhexidine solution and draped in sterile fashion. After subcutaneous administration of lidocaine, the right portal vein is punctured from a lateral approach using ultrasound and fluoroscopic guidance with a 21-gauge Chiba needle. The needle is exchanged over a 0.018-inch guide wire (Fig. 1A) for a 4F Kumpe end-hole catheter (Fig. 1B), which is advanced into the main portal vein.

Portal venography is performed using iso-osmolar contrast to confirm position (Fig. 1C). The islet preparation is resuspended in medium that contains 20% human albumin and heparin (35 U/kg recipient body weight if pellet volume is < 5 mL; 70 U/kg recipient body weight if pellet is 5 to 10 mL). Islets are infused via the Kumpe catheter directly into the main portal vein (Fig. 1D). The infusion is performed over ~30 minutes with portal vein pressure monitoring throughout. Specifically, the portal pressure is measured and recorded at time of initial access, after half the infusion of each bag, at the completion of each bag, at the completion of the infusion of the wash of each bag, 5 to 10 minutes after completion of all infusions, and for any change in patient symptoms, focusing particularly on changes in epigastric pain as measured by a pain scale.

The infusion is terminated if the (1) opening pressure is greater than 20 mm Hg, portal pressure rises to above 22 mm Hg and does not fall below 18 mm Hg within 30 minutes of the observed 22 (or greater) mm Hg pressure; (2) the opening pressure doubles and remains below 18 mm Hg and does not fall below 15 mm Hg within 30 minutes (if the pressure does fall to below 15 mm Hg, islet infusion will continue slowly); (3) at any time during the infusion process, the portal pressure is observed to be > 22 mm Hg for a period of greater than 10 minutes; or (4) subject symptoms become intolerable; or (5) the patient requests cessation of infusion.

After the infusion, the Kumpe catheter is retracted to the portal vein entry point (Fig. 1E) and the tract embolized using metal coils and gelfoam plugs (Fig. 1F) deposited just outside the portal vein entry point (Fig. 1G,H). It is important to recognize that contrast is toxic to islet cells so it cannot be used after the initial portal venogram.

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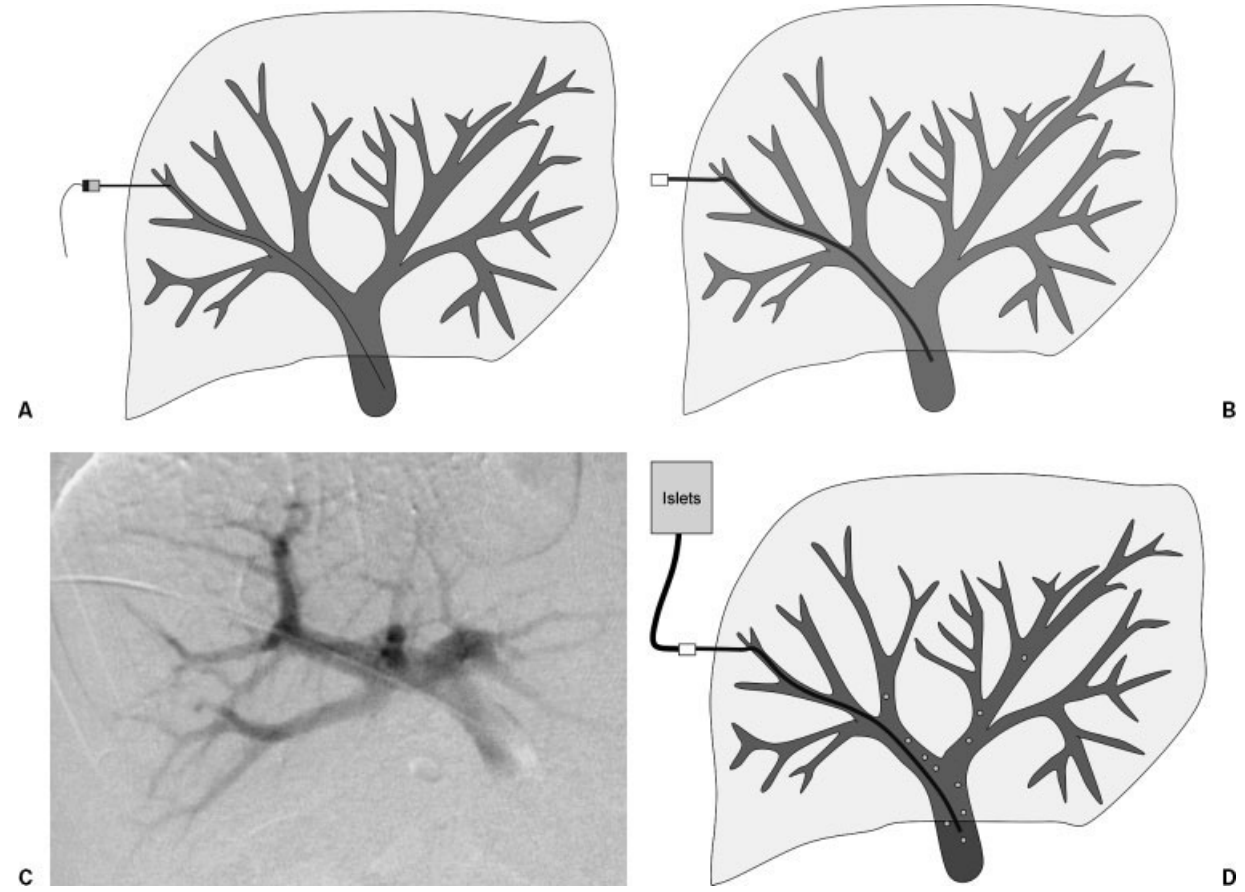

Figure 1 Islet cell transplantation. (A) The portal vein is accessed using a 21-gauge needle and a 0.018-inch guide wire is advanced into the portal vein. (B) The needle is exchanged for a 4F catheter. (C) Digital subtraction portal venogram showing patency of portal vein. (D) Islets are infused with intermittent pressure monitoring.

Postprocedure

The patient is observed overnight and discharged to home the next day. Anticoagulation is continued for 7 days using low molecular weight heparin injections. Immunosuppressive therapy with drugs such as sirolimus (Wyeth Ayerst, Madison, NJ), tacrolimus (Fujisawa, Deerfield, IL), and daclizumab (interleukin-2 receptor monoclonal antibody; Hoffman–La Roche, Inc., Nutley, NJ) is initiated.

DISCUSSION

There are two transplantation options for treatment of type 1 diabetes: whole organ transplantation and islet cell infusion. Organ transplantation currently offers the best allocation of limited organs as one organ can often be used in two recipients. In contrast, it is uncommon to harvest a critical mass of islet cells from one donor unless a large donor pancreas is used in a small recipient. Thus the procedure is typically repeated until enough islet cells have been transplanted to achieve insulin independence.

Islet cell transplantation offers a minimally invasive option with cells infused directly into the portal vein. This procedure has low complication rates and morbidity but is typically reserved for brittle diabetics who have history of hypoglycemic unawareness or progressive complications of diabetes such as nephropathy, retinopathy, or neuropathy. The most technically difficult portion of islet transplantation is the harvest method, which requires an automated procedure for islet isolation and continuous density gradients for separating exocrine fragments from islets. The islets must be highly purified to be suitable for transplantation to reduce risk of thrombotic complications in the portal vein. Other possible complications include perihepatic or intraparenchymal hepatic hemorrhage and hemothorax. It is important to recognize that patients are fully anticoagulated after infusion and are therefore at increased risk for bleeding. The tract is embolized prior to catheter removal to limit this risk. After transplantation, immunosuppressive therapy is initiated.

Islet cell transplantation first gained recognition in the 1970s in experiments with rodents. Unfortunately, it was only recently that the procedure has been successful in humans. From 1990 until 1995, only 6% of islet transplants were successful. The landmark

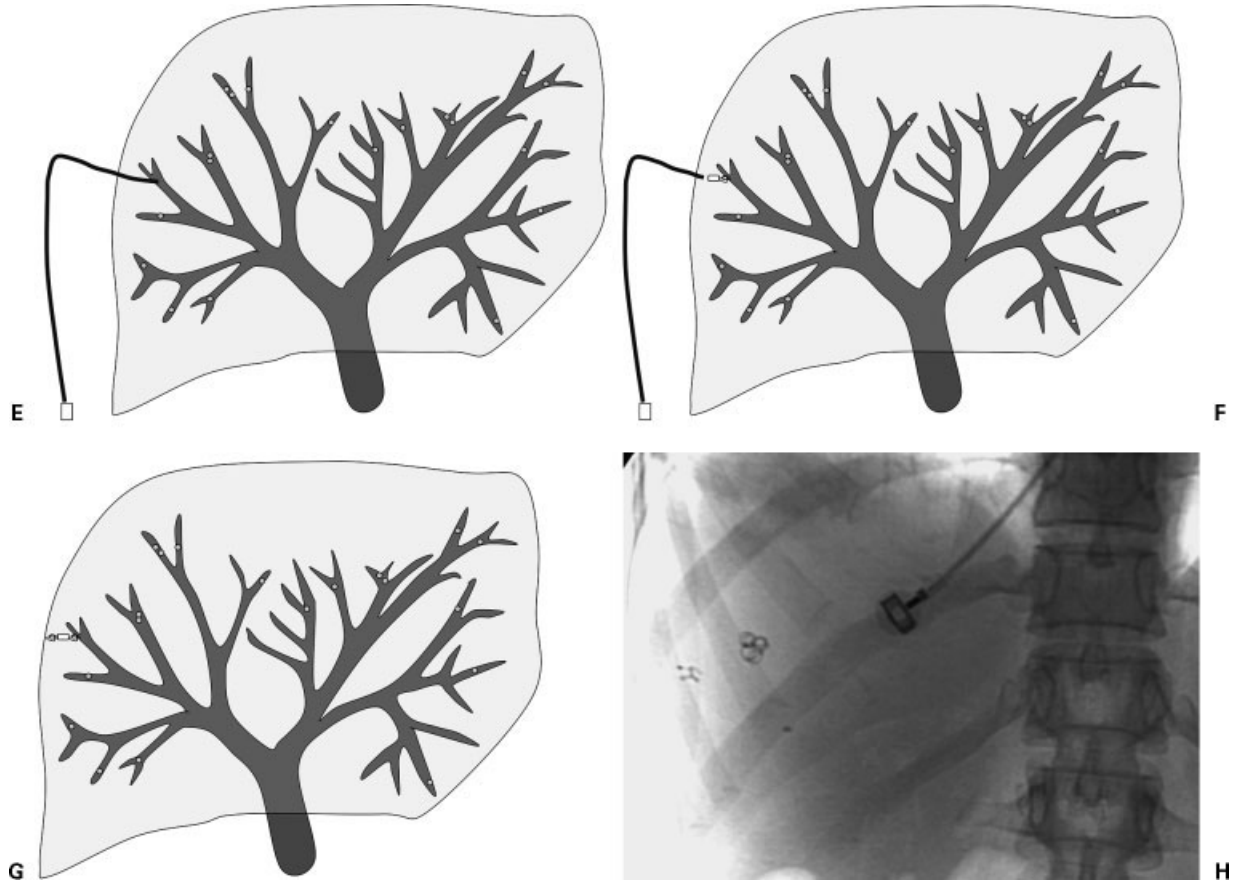

Figure 1 (E) After infusion, the catheter is retracted to the entry site. (F) The tract is embolized with gelfoam and coils. (G) Completed transplant with embolization of parenchymal tract. (H) Final fluoroscopic image after embolization of tract.

Edmonton study published in 2000 by Shapiro and colleagues in the *New England Journal of Medicine* described success in seven consecutive patients who maintained normal blood sugar levels for an average of 1 year. Their success can be attributed to three factors. First, these investigators transplanted islets soon after harvest and eliminated glucocorticoids from immunosuppressive regimens. Second, they decreased the dose of tacrolimus and added daclizumab. Finally, they repeated the infusion procedure until patients received a critical mass of islet cells, enabling them to maintain normoglycemia without exogenous insulin. Since this study, there has been extensive renewed interest in the islet cell transplantation with many centers throughout the world performing this procedure. In the future, the use of xenografts or stem cells could ameliorate organ shortages and lead to more widespread use of this technique.

SUGGESTED READINGS

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